Markman Presentation for Medicis and Valeant

ALLERGAN USA, INC., and ALLERGAN INDUSTRIE, SAS,
Plaintiffs,
v.
MEDICIS AESTHETICS, INC., et al.,
Defendants

Introduction to Dermal Fillers

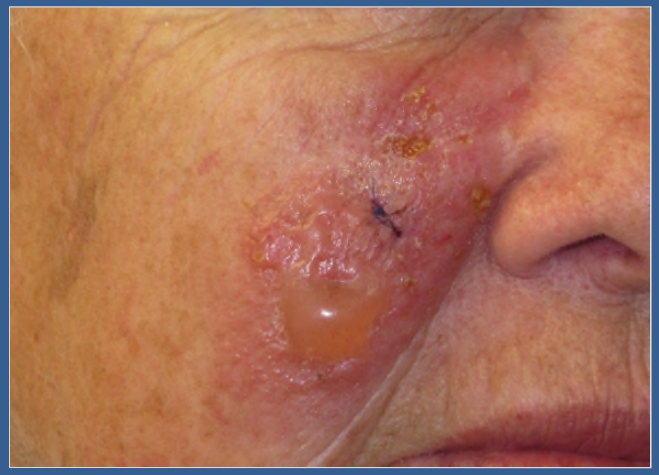
Before

After

- Dermal fillers are one of the most popular, nonsurgical options solving problems related to aging skin.
- Also known as “injectables” or “soft-tissue fillers.”
- They fill in the area under the skin, making wrinkles less apparent.

Source: http://www.restylaneusa.com/What-is-Restylane/Restylane-Restylane-L, downloaded 6/27/14

Collagen Dermal Fillers



- The initial collagen fillers included Zyderm/Zyplast & Fibrel
- These had numerous shortcomings:
  - Potential for allergy to bovine collagen required skin testing before treatment
  - Results lasted 3 months or less
  - Human collagen significantly reduces allergen risk, but doesn't fix degradation problem

US Patent App No. 2006/0040894, Hunter

Prior Art Use of HA as Dermal Filler

boxymethyl cellulose all at 10 mg/ml. In order to attain this concentration a dose of approximately 10 times that required dose per ml may be needed (e.g., a total weight of 10 mg indomethacin, 20 mg of sulphated polysaccharides, 100 mg of propylene glycol, TRITON, PEG, SPAN, PLURONIC or carboxymethyl cellulose) in an area or volume that may be exposed to a few ml of aqueous body fluid. So, for example, if 1 ml of an HA solution was injected where the injection fluid may be exposed to perhaps 2 ml of interstitial fluid diffusing past the area then a dose of 100 mg of each of these inhibitors would be recommended to ensure attainment of a dose of 10 mg per ml for some time after. The dosing needs depend largely of the injection volume and the site of application. At sites with a higher fluid turn over, more hyaluronidase inhibitor may be given. Furthermore, if the inhibitor was released in a controlled manner from a polymeric dosage form then the applied total dose may be calculated by one skilled in the art based on inhibitor release profiles, site of application, turn over of body fluid in that area and other parameters such as age and general health.

[0177] 4. HI-Loaded Hyaluronic Acid Cosmetic Implants

[0178] A variety of injectable hyaluronic acid products have been developed for soft tissue augmentation to correct facial scars, diminish facial lines and augment the lips. Specifically, such implants are indicated for the treatment of a variety of contour deficiencies including (but not restricted to) correction of acne scars, atrophy from disease or trauma, glabellar frown lines, nasolabial folds, or defects secondary to rhinoplasty, skin graft or other surgery and other soft tissue defects. Manufactured synthetic hyaluronic gels commercially available for this purpose include RESTYLANE and PERLANE and HYLAFORM (also known as HYLAN B) from Genzyme Corporation. Other examples of commercial HA products that may be combined with an HI for use in cosmetic injections include: ACHYAL from Meiji Seika Kaisha, Ltd. (Japan), JUVEDERM from L.E.A. Derm (France), MACDERMOL from Laboratoires O.R. GE V. MacDermol (France), and ROFILAN Hylan Gel from Rofil Medical International (Holland).

[0179] Unfortunately, repeated "touch up" procedures are often required as the implant is colonized by host connective tissue cells and inflammatory cells which produce hyaluronidase and other enzymes capable of breaking down the HA implant over time. An injectable hyaluronic acid containing a hyaluronidase inhibitor (HI), both alone or in a sustained release preparation, can result in increased durability of the implant and reduce the number of subsequent repeat injections. Although any of the previously described hyaluronidase inhibitors may be suitable for incorporation into a dermal HA injection, the following are particularly preferred: aurothiomalate, indomethacin, propylene glycol, dextran sulphate, fucoidan, bederagenin, flavonoids, agents that modulate allergic reactions, phenolic compounds, and carboxymethyl cellulose.

[0180] Regardless of the formulation utilized, administration of the HI-loaded HA injection may proceed in the following manner. A pre-loaded syringe with a fine gauge needle (30 or 32 gauge) containing the HI-HA implant material is used. The patient is placed in a sitting position with the table back slightly reclined. Topical lidocaine and/or prilocalne can be used for anesthesia. The needle is inserted at an angle to the skin and advanced into the superficial dermal tissue. A sufficient amount of implant material is extruded to repair the soft tissue contour defect. In the case of HI-loaded RESTYLANE, overcorrection (injection of more material than is ultimately needed) is required as some of the injected material dissipates in the hours following injection. HI-loaded PERLANE is typically used to correct deeper lines and is injected deeper into th dermis.

[0181] Representative examples of hyaluronic acid con positions used in cosmetic surgery injections are describe in U.S. Pat. Nos. 5,633,001; 5,256,140; and 6,703,041.

[0182] The HI may be combined with a polymer system t provide sustained release of the agent as part of an H dermal injection. The material suitable for delivery of a H agent for the purposes of this invention can be composed a non-degradable or a degradable material; however, degradable material is preferred. Suitable degradable mat rials include, but are not limited to, crosslinked materials PEG, gelatin, collagen, GELFOAM, polysaccharides, ca bohydrates, proteins (e.g., albumin, casein, whey protein plant proteins, fish proteins etc), alginates, starch, cellulo derivatives (HPC etc), cellulose, cellulose esters, blends an copolymers thereof, chitosan, chitosan derivatives, polyc ter-polyalkylene oxide block copolymers (e.g., PLGA-PEG PLGA, MePEG-PLGA, etc), degradable polyesters, polyan hydrides, polyorthoesters, polyphosphoester polyphosphazines, cyanoacrylate polymers, injectable PEG containing formulations such as COSEAL, FOCALSEAL SPRAYGEL, DURASEAL or compositions comprising pentaerythritol poly(ethylene glycol)ether tetra-sulfhydry (4-armed thiol PEG), pentaerythritol poly(ethylene glyc l)ether tetra-succinimidyl glutarate] (4-armed NHS PEG and methylated collagen, such as described in U.S. Pat. No 5,874,500; 6,051,648; 6,166,130 and 6,312,725, fibrinogen containing formulations such as FLOSEAL or TISSEAL REPEL or FLOWGEL, and other low molecular weigh polymers that can be excreted.

[0183] The HA-HI composition may further comprise a anesthetic such as lidocaine, benzocaine or prilocalne and/o a neurotoxin such as a botulinum toxin.

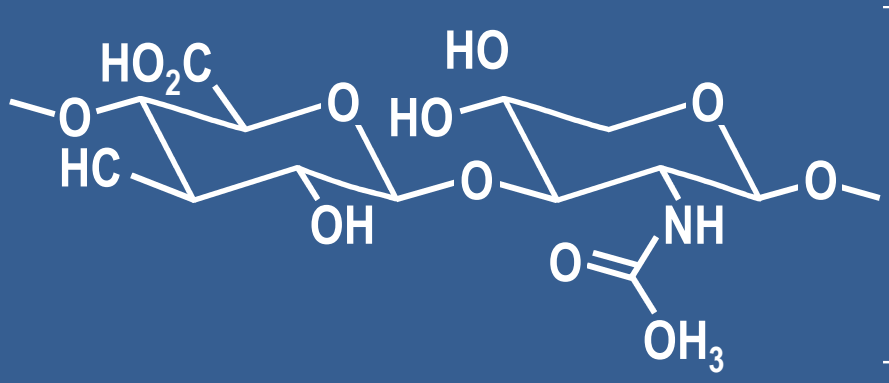
[0184] It should be apparent to one of skill in the art th potentially any hyaluronidase inhibitor may be utilize alone, or in combination, in the practice of this embodime as described above. Exemplary HI agents for use in com bination with HA in cosmetic injection procedures includ aurothiomalate, indomethacin, propylene glycol, carboxym ethyl cellulose, dextran sulphate, fucoidan and heparin, well as analogues and derivatives of the aforementioned.

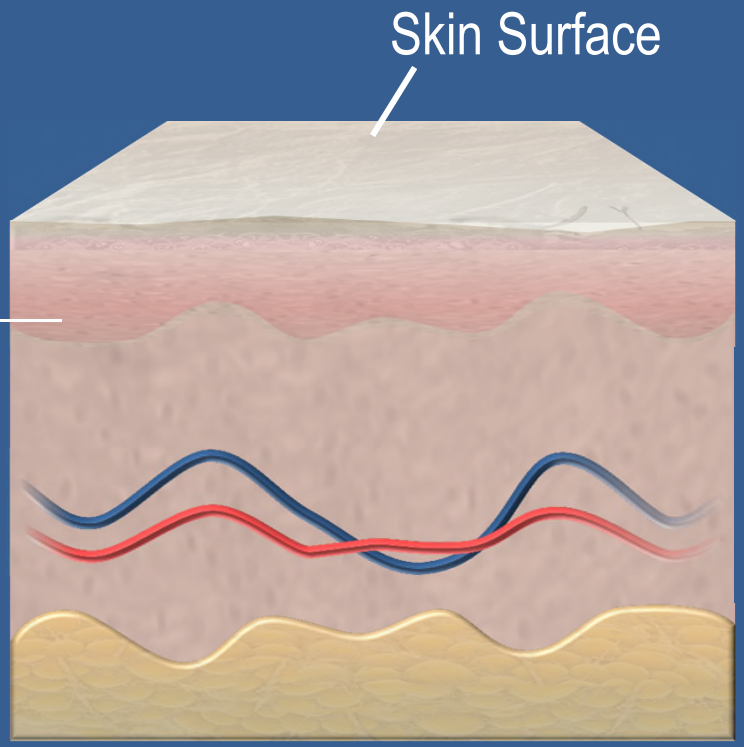
[0185] Suitable doses of these compounds may be such a to provide a steady concentration of each agent to elicit prolonged inhibitory effect on hyaluronidase. These concen trations are approximate and may be adjusted depending the potency of the compound and duration of effect require aurothiomalate 10 mM, indomethacin 1 mg/ml, heparin mg/ml, sulphated polysaccharides 2 mg/ml, and propylen glycol, TRITON X-100, PEG, SPAN, PLURONIC L10 and carboxymethyl cellulose all at 10 mg/ml. In order t attain this concentration a dose of approximately 10 time that required dose per ml may be needed (e.g., a total weight of 10 mg indomethacin, 20 mg of sulphated polysaccharides, 100 mg of propylene glycol, TRITON, PEG, SPAN, PLURONIC or carboxymethyl cellulose) in an area that may be

[0178] A variety of injectable hyaluronic acid products have been developed for soft tissue augmentation to correct facial scars, diminish facial lines and augment the lips. Specifically, such implants are indicated for the treatment of a variety of contour deficiencies including (but not restricted to) correction of acne scars, atrophy from disease or trauma, glabellar frown lines, nasolabial folds, or defects secondary to rhinoplasty, skin graft or other surgery and other soft tissue defects. Manufactured synthetic hyaluronic gels commercially available for this purpose include RESTYLANE and PERLANE and HYLAFORM (also known as HYLAN B) from Genzyme Corporation. Other examples of commercial HA products that may be combined with an HI for use in cosmetic injections include: ACHYAL from Meiji Seika Kaisha, Ltd. (Japan), JUVEDERM from L.E.A. Derm (France), MACDERMOL from Laboratoires O.R. GE V. MacDermol (France), and ROFILAN Hylan Gel from Rofil Medical International (Holland).

Source: US Patent App No. 2006/0040894, p. 21, par. 0178

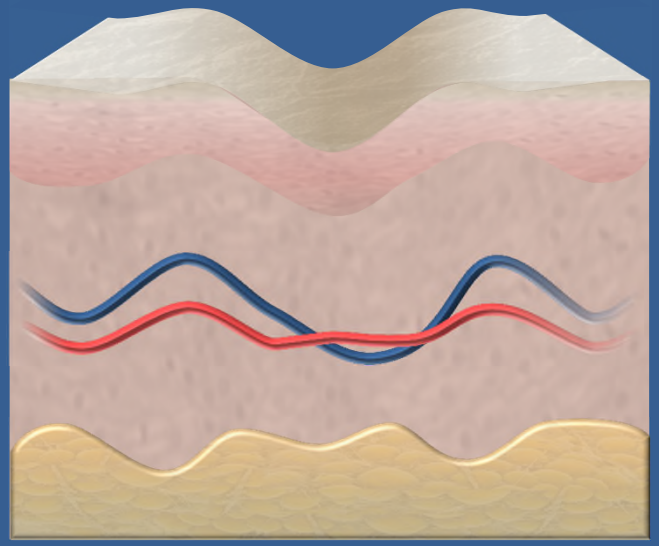
Hyaluronic Acid





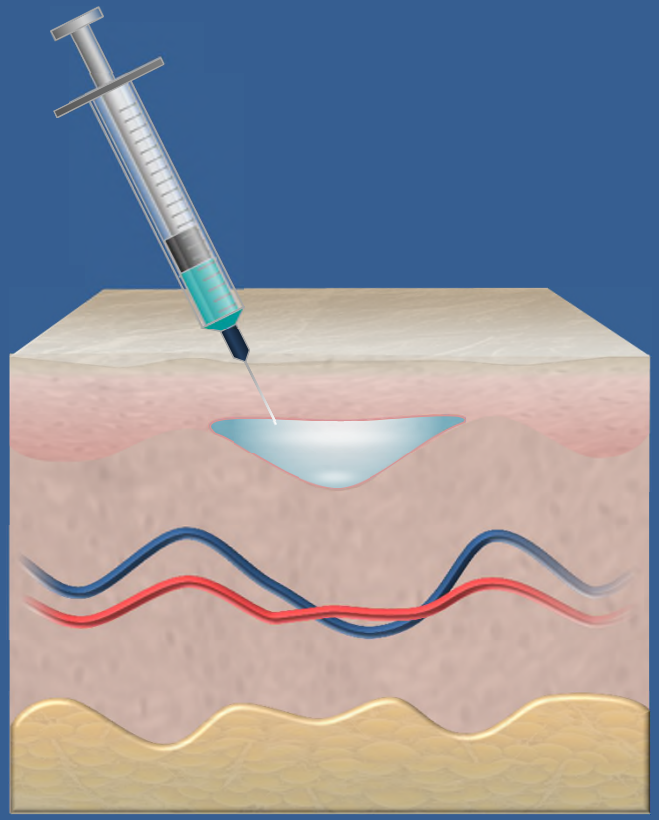
Hyaluronic acid is naturally present in the human body

Benefits of Hyaluronic Acid



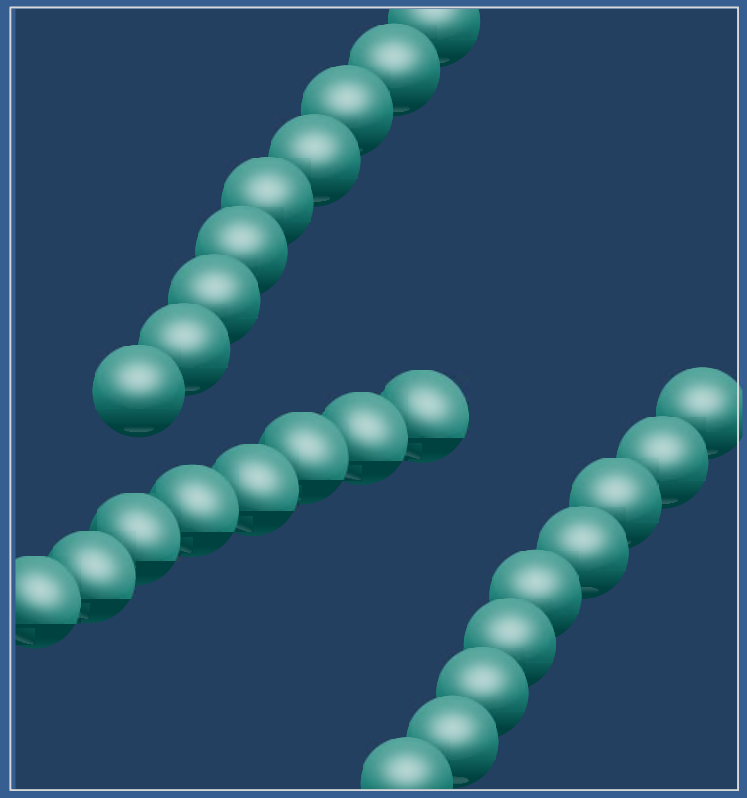
- Unlike collagen, hyaluronic acid minimizes the risk of allergic reactions
- It can bind to large amounts of water
- Excellent volumizer

Benefits of Hyaluronic Acid

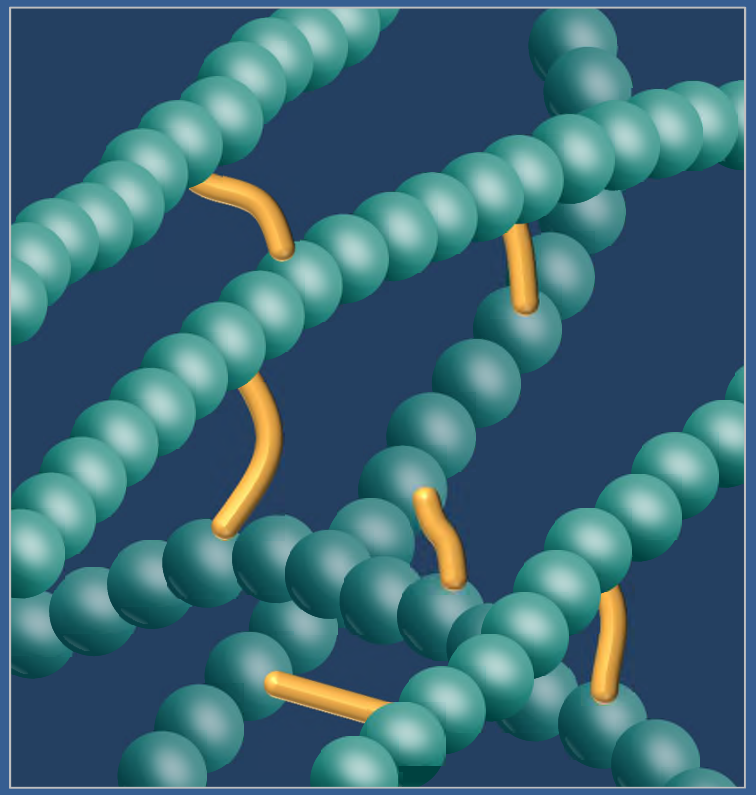


- Unlike collagen, hyaluronic acid minimizes the risk of allergic reactions
- It can bind to large amounts of water
- Excellent volumizer
- Crosslinked hyaluronic acid can last much longer than collagen

Crosslinking Process

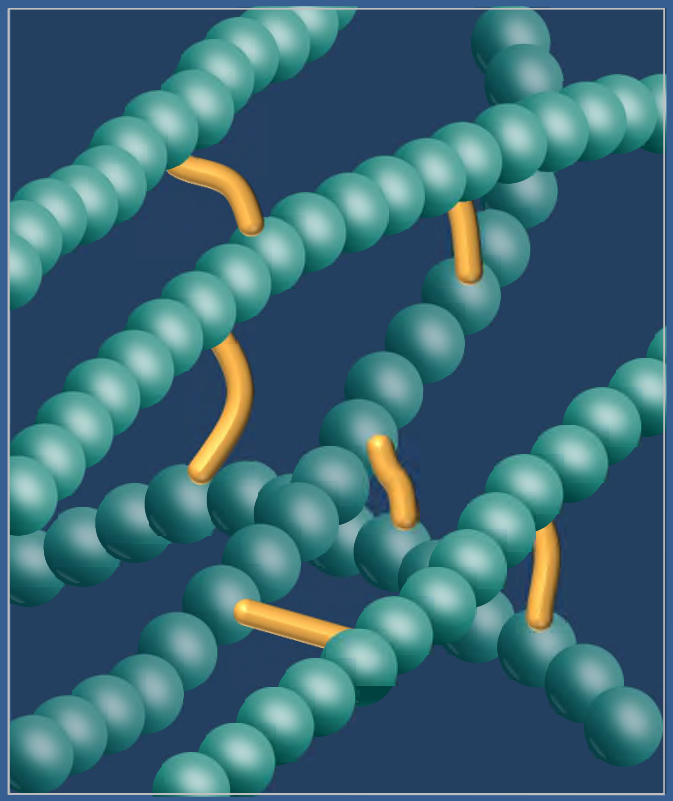


Free HA



Crosslinked HA

Major Crosslinking Agents Used with HA



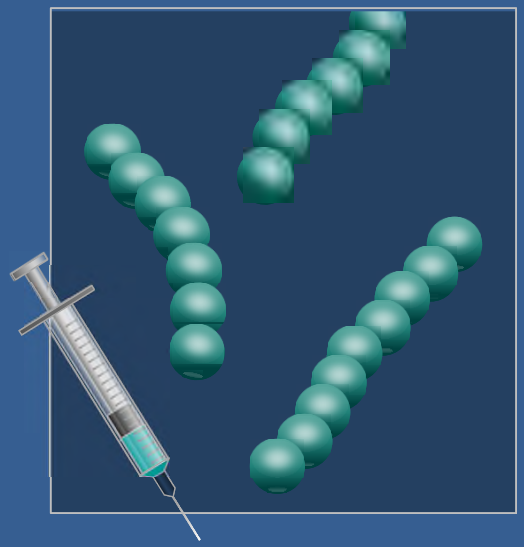
1,4-butanediol diglycidyl ether (BDDE)

1,2,7,8-deipoxyoctane (DEO)

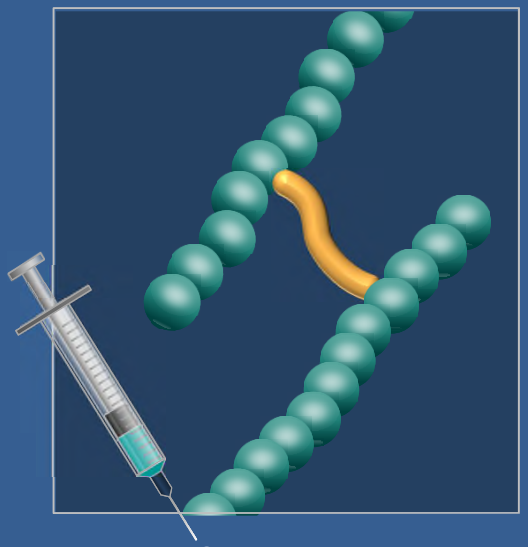
biscabodiimide (BCDI)

divinyl sulfone (DVS)

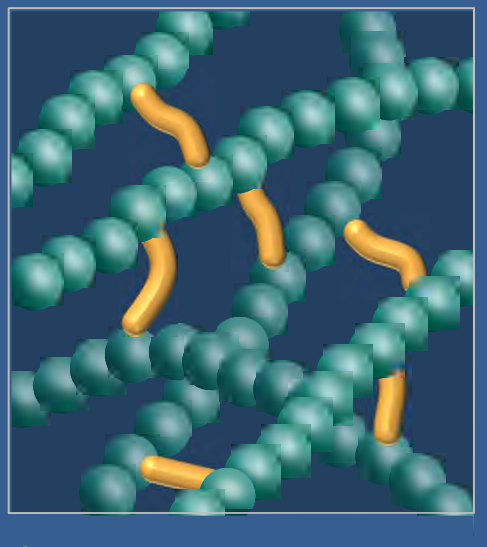
Complication of Purely Crosslinked Hyaluronic Acid



Uncrosslinked HA
Easy to Inject



Lightly Crosslinked HA
Easy to Inject



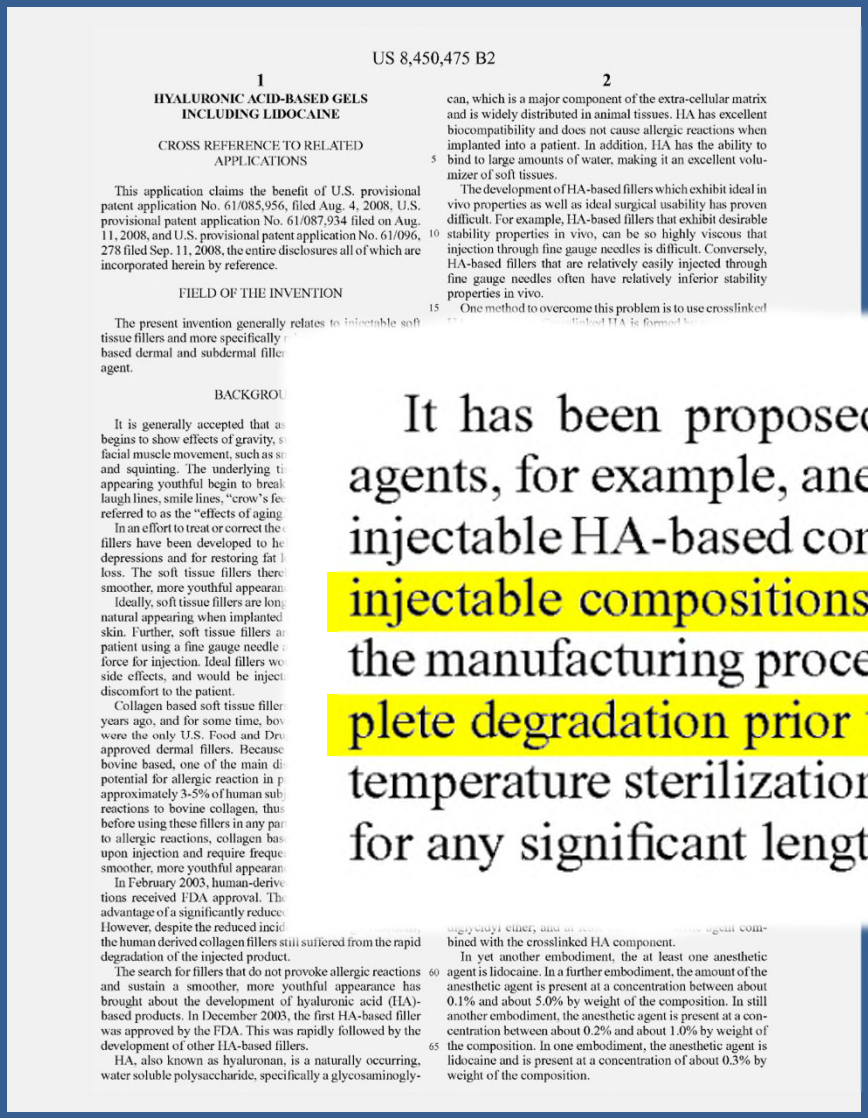
Crosslinked HA
Difficult to Inject

Issues With Crosslinking

- Difficult to inject
- Injections can cause discomfort
- Potential solutions:
  - Add uncrosslinked HA
  - Use of an anesthetic

Lebreton Patents-in-Suit

Unsupported Concern Regarding HA and Lidocaine Product



US 8,450,475 B2

1

HYALURONIC ACID-BASED GELS INCLUDING LIDOCAINE

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. provisional patent application No. 61/085,956, filed Aug. 4, 2008, U.S. provisional patent application No. 61/087,934 filed on Aug. 11, 2008, and U.S. provisional patent application No. 61/096,278 filed Sep. 11, 2008, the entire disclosures all of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention generally relates to injectable soft tissue fillers and more specifically
based dermal and subdermal filler
agent.

BACKGRO

It is generally accepted that as
begins to show effects of gravity,
facial muscle movement, such as
and squinting. The underlying
appearing youthful begin to break
laugh lines, smile lines, "crow's fe
referred to as the "effects of aging
In an effort to treat or correct the
fillers have been developed to he
depressions and for restoring fat
loss. The soft tissue fillers there
smoother, more youthful appearan
Ideally, soft tissue fillers are long
natural appearing when implanted
skin. Further, soft tissue fillers a
patient using a fine gauge needle
force for injection. Ideal fillers wo
side effects, and would be inject
discomfort to the patient.
Collagen based soft tissue filler
years ago, and for some time, bov
were the only U.S. Food and Dru
approved dermal fillers. Because
bovine based, one of the main di
potential for allergic reaction in p
approximately 3-5% of human sub
reactions to bovine collagen, thus
before using these fillers in any pa
to allergic reactions, collagen bas
upon injection and require freque
smoother, more youthful appearan
In February 2003, human-derive
tions received FDA approval. Th
advantage of a significantly reduce
However, despite the reduced incid
the human derived collagen fillers still suffered from the rapid degradation of the injected product.

The search for fillers that do not provoke allergic reactions and sustain a smoother, more youthful appearance has brought about the development of hyaluronic acid (HA)-based products. In December 2003, the first HA-based filler was approved by the FDA. This was rapidly followed by the development of other HA-based fillers.

HA, also known as hyaluronan, is a naturally occurring, water soluble polysaccharide, specifically a glycosaminoglycan, which is a major component of the extra-cellular matrix and is widely distributed in animal tissues. HA has excellent biocompatibility and does not cause allergic reactions when implanted into a patient. In addition, HA has the ability to bind to large amounts of water, making it an excellent volumizer of soft tissues.

The development of HA-based fillers which exhibit ideal in vivo properties as well as ideal surgical usability has proven difficult. For example, HA-based fillers that exhibit desirable stability properties in vivo, can be so highly viscous that injection through fine gauge needles is difficult. Conversely, HA-based fillers that are relatively easily injected through fine gauge needles often have relatively inferior stability properties in vivo.

One method to overcome this problem is to use crosslinked

bined with the crosslinked HA component.

In yet another embodiment, the at least one anesthetic agent is lidocaine. In a further embodiment, the amount of the anesthetic agent is present at a concentration between about 0.1% and about 5.0% by weight of the composition. In still another embodiment, the anesthetic agent is present at a concentration between about 0.2% and about 1.0% by weight of the composition. In one embodiment, the anesthetic agent is lidocaine and is present at a concentration of about 0.3% by weight of the composition.

2

It has been proposed to incorporate certain therapeutic agents, for example, anesthetic agents such as lidocaine, into injectable HA-based compositions. Unfortunately, HA-based injectable compositions which incorporate lidocaine during the manufacturing process are prone to partial or almost complete degradation prior to injection, particularly during high temperature sterilization steps and/or when placed in storage for any significant length of time.

Source: '475 patent, 2:20-27; '795 patent, 2:20-27

5,731,298 Patent, Reinmuller (1998)

HA and Lidocaine in the Prior Art

EXAMPLE 1

Production of an injectable gel from the following components:

Component	Amount
cross-linked hyaluronic acid ("Hylagel" Biomatrix Co., NJ, USA)	0.004 g
lidocaine hydrochloride	0.02 g
water, purified (DAB 9)	to 1.0 g

The components are dissolved under a nitrogen atmosphere while stirring and briefly heating; a colourless clear gel is obtained after cooling; pH value: 7.00±0.1.

The gel is dispensed into pressure-resistant piercable ampoules and sealed. Afterwards a heat sterilization is carried out and the gel is stored protected from light.

Application example 1

The treatment of a ca. 3 cm×5 cm dark-red raised keloid is described which was present on the back of a 30 year old woman after a tangential cut by a broken pane of glass.

The patient complained about itching in the area of the keloid. The keloid was infiltrated with cross-linked hyaluronic acid (Hylon) by injection for a total of four times at intervals of 4 to 8 weeks. The itching had already disappeared a few hours after the first injection. The keloid became considerably paler within two weeks and a flattening was already recognizable after four weeks. After ca. 6 months there was a pale, only slightly raised scar.

Application example 2

The treatment of a keloid in the lower fold of the breast (right and left) is described which occurred in a female patient after surgical breast correction.

The keloids were treated several times using conservative methods (topical preparations) and repeatedly excised. After the last excision, cross-linked hyaluronic acid was injected during the operation into the wound edges on the right side. Then both sides were sutured identically. The sutures were removed on the right and left side after two weeks. After four weeks the untreated scar on the left side was raised considerably more and was more reddened than the scar on the right side treated with hyaluronic acid. In addition it was possible to successfully prevent the reoccurrence of a keloi on the right-hand side. This also demonstrates the preventiv effect of the pharmaceutical preparation according to th invention.

I claim:

1. A method for treating a pre-existing scar or pre-existin keloid comprising injecting a composition comprising pharmaceutically effective amount of a cross-linked hyalu ronic acid in combination with a pharmaceutically accept able carrier into the pre-existing scar or pre-existing keloi wherein the pharmaceutically effective amount of a cross linked hyaluronic acid is 0.1% to 20% by weight of th composition.

2. A method for treating a scar or keloid according t claim 1, wherein said cross-linked hyaluronic is cross-linke by chemical cross-linking, chelate formation, complex for mation or salt formation.

3. A method for treating a scar or keloid according t claim 1, wherein said cross-linked hyaluronic acid is cross linked by chemical cross-linking.

* * * * *

EXAMPLE 1

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The gel is dispensed into pressure-resistant piercable ampoules and sealed. Afterwards a heat sterilization is carried out and the gel is stored protected from light.

Source: '298 patent, 7:1-18

US Patent App. No. 2005/0136122, Sadozai

HA and Lidocaine in the Prior Art

[0061] The rate of delivery of a bioactive agent is related not only to the rate of its diffusion, but also to the rate of degradation of the HA in which the drug or other bioactive agent is dispersed. The rate of degradation of the HA is related to the degree of cross-linking and is also dependent on numerous metabolic processes taking place in vivo. The degradation process is usually slower than diffusion. By choosing the concentration of the drug dispersed within the HA, and the degree of cross-linking, the rate of degradation and diffusion and, thus, the rate of drug delivery, can be controlled.

[0062] As used herein, a "physiologically effective amount" is the amount of bioactive agent that is sufficient to have the intended effect, e.g., an amount of local anesthetic sufficient to have an anesthetic effect in a subject injected with a composition including the agent. One skilled in the art will be able to determine a physiologically effective amount based on the amount of composition employed, the subject's medical history, and the like. The drug concentration can be varied over very broad limits and preferably should be chosen depending on the degree of cross-linking of the HA, the solubility of the drug, its pharmaceutical activity, and the effect desired.

[0063] As used herein, a "physiologically acceptable solution" is any solution known in the art that is useful as a carrier in a physiological system, e.g., aqueous solutions that are typically sterile, non-allergenic, non-toxic, and the like, e.g., a saline solution, a buffer solution, a sugar solution, and the like.

[0064] The viscolastic properties of the composition can be determined as shown in the Examples. In one embodiment, the composition has at least one parameter measured at 37° C. selected from a storage modulus G' of at least about 50 Pa (Pascals) when measured at 1 Hz (Hertz) frequency using a 4 cm (centimeter) flat geometry; and a kinematic viscosity of at least about 20,000 cPs (centiPoise) when measured at a shear rate of 1 s^{-1}.

[0065] In other embodiments, kinematic viscosity is at least about 40,000 cPs, more typically at least about 60,000 cPs, and preferably at least about 70,000 cPs. In another embodiment, the kinematic viscosity is from about 20,000 cPs to about 250,000 cPs. In other embodiments, the kinematic viscosity is from about 40,000 cPs to about 220,000 cPs, more typically from about 60,000 cPs to about 200,000 cPs, and preferably from about 70,000 cPs to about 170,000 cPs.

[0066] In other embodiments, the storage modulus G' is at least about 100 Pa, typically at least about 100 Pa, more typically at least about 200 Pa, and preferably at least about 400 Pa. In other embodiments, the storage modulus G' is from about 50 Pa to about 1,600 Pa, typically from about 100 Pa to about 1,200 Pa, more typically from about 200 Pa to about 1000 Pa, and preferably from about 400 Pa to about 700 Pa.

[0067] The crosslinked HA composition can be characterized by its biostability, e.g., its resistance to degradation in vitro by hyaluronidase enzyme as shown in the Examples. For example, upon combining the composition at 37° C. with hyaluronidase enzyme in an amount of about 0.3% by weight, under conditions suitable for reaction with hyaluronidase, the value of G' for the composition measured after about 16 hours of reaction is at least about 5% of

of G' measured at about

embodiments, the value

after about 16 hours of

G' measured at about 15

about 10%, or at least a

at least about 50%, ty

typically at least about

80%. In one embodime

tion measured after abo

same as the value of

reaction.

[0068] In other embo

increased, e.g., the com

sion of a local anesthe

non-stabilized composit

except that the local an

embodiments, the stabi

tions can be compared

the same conditions. A

hydrating dehydrated p

tions disclosed herein w

anesthetic (e.g., lidocain

for a non-stabilized com

110%, typically at least

about 150%, and prefer

[0069] In a particular

includes crosslinked, w

ticles. The particles in

ticles have an average

consisting of a hydrated

about 20 and about 10

average diameter betw

Further, the particles in

following structural for

HA'—U—R,—U—HA

[0070] wherein the v

above. The composition

at 37° C. selected from a

50 Pa when measured a

geometry, and a kinema

cPs when measured at

composition is sufficien

that upon combining th

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under conditions suitab

the value of G' for the c

of reaction is at least ab

at less than about 15 m

ment, the value of G' fo

hours of reaction is at

measured at less than a

[0071] As used herein

means that a subject has

from application of the

e.g., the subject is in ne

conditions, e.g., wrink

wrinkles in the skin, typ

eyes, nose and lips, cor

defects and depressed sc

tary or acquired through

plications, and the like.

[0025] The invention is directed to crosslinked HA compositions, their preparation, and their methods of use.

...

[0068] In other embodiments, the storage modulus G' is increased, e.g., the composition is stabilized, by the inclusion of a local anesthetic, e.g., lidocaine, compared to a non-stabilized composition, e.g. an identical composition except that the local anesthetic is not included. For these embodiments, the stabilized and non-stabilized compositions can be compared by measuring the value of G' under the same conditions. A stabilized composition prepared by hydrating dehydrated particles under the hydration conditions disclosed herein with a solution having 0.1% of a local anesthetic (e.g., lidocaine) by weight has a G' greater than G' for a non-stabilized composition of generally at least about 110%, typically at least about 120%, more typically at least about 150%, and preferably at least about 175%.

Source: US Patent App. No. 2005/0136122, p.2, par. 0025 and p. 6, par. 0068

US Patent App. No. 2005/0136122, Sadozai

HA and Lidocaine in the Prior Art

addition of the enzyme. The storage modulus G' of the gel was recorded at 10 min intervals for 16 hours at a temperature=37° C., a flat plate measuring geometry, a gap of 200 μm, and a frequency of 1 Hz. **FIG. 5** shows G' for each product versus time. As can be see, the rate of loss representing the susceptibility of the product to enzymatic hydrolysis for the invention is much less than that of the three competing compositions.

Example 20

ΔG'/Δt of Compositions Versus Hyaluronidase is Independent of G'

[0106] **FIG. 6** shows ΔG'/Δt over a 16 h period for a range of crosslinked HA compositions having initial storage modulus values between about 200 to about 1200 Pa. The compositions are prepared and the measurements conducted according to the preceding Examples. As can be seen, the degradation of the crosslinked HA compositions is essentially independent of initial storage modulus G' over this 16 hour period.

Example 21

Synergistic Effect of Lidocaine on Rheological Properties of the Gel

[0107] Lidocaine can have a synergistic effect and increase the initial storage modulus G' of the gel compared to otherwise identical compositions prepared in a buffer without lidocaine. Crosslinked HA of Example-5 was processed as in Example-12 using three separate phosphate buffers 1 (no lidocaine), 2 (0.2% lidocaine), and 3(0.3% lidocaine). Gels were made to 32-mg/mL concentrations and the storage modulus G' and degradation profile ΔG'/Δt of each was measured according to the method described in Example-12. **FIG. 7** shows that the compositions with lidocaine have a significantly higher modulus G' over the time of the test. Thus, crosslinked HA with lidocaine can have good biostability, and can in some cases have a synergistic effect, increasing G'.

Example 22

Invention is Effective for Tissue Augmentation

[0108] The crosslinked HA product used in the study was prepared according to the procedure described in Example 14. In an Interdermal Injection Study in the Guinea Pig Model, the crosslinked HA product and a control article, (ZYDERM™ II, Collagen, Palo Alto, Calif.), were injected intradermally. Each injection site (6 per time interval per sample) was measured for height and diameter at 2, 4-, 8 and 12-weeks. Specimens were explanted for histological evaluation at each time interval.

[0109] Twelve guinea pigs were included in this study and assigned to a termination interval of two animals each at 2, 4, 8, 12, 18, and 24 weeks.

[0110] The right and left flank of each animal was clipped free of fur at least 1 hour before dosing. Each animal received six intradermal injections, three per side. The test article and control article were randomized over each animal. Both articles were dosed at 0.2 cc per site. Each site was marked with a non-toxic marker and injection sites were approximately 2 cm apart. In addition, each site was measured for height and diameter at each interval. The measurements immediately after injection were assigned a score of "0". An increase in height and diameter indicated edema.

[0111] At each termination interval, three animals were euthanized, the fur clipped, injection site measured, and the site removed and fixed in 10% neutral buffered formalin. The excised tissues were embedded, cut and stained with hematoxylin and eosin (H & E), and examined by a qualified pathologist. Specimens were examined for the presence of the injected article and for any tissue response.

[0112] During the first week of the study, erythema scores were minimal (slight) and equally distributed between the test article and Zyderm II injection sites. Edema scores were inconsistent and equally distributed between the two materials. During week two, erythema scores were similar to week one. Edema scores were reduced with most dropping to zero. Injection site measurements at 4-weeks were equivalent to measurements taken immediately after injection.

[0113] The volume of CTA was unchanged from 2 weeks to 4 weeks. At 8-weeks observation time, nearly all test article sites continued to maintain height and diameter measurements. Conversely, nearly all control sites were unmeasurable. At 12-weeks observation time, test article was flattened and extended laterally in all sites. However, in the more tissue dense areas of the dermis, the test article did not spread out to the degree as in the less dense areas. Fibroblasts and adipose tissue were located through out the test article at approximately the same density as the tissues adjacent to the injection site. The control article was not identified in any of the injection sites.

[0114] Microscopic examination showed no cellular response to test article and only a minor macrophage infiltrate in the control article at 2-weeks and 4-weeks. At 8-weeks and 12-weeks, there was no observable cellular response to either material.

[0115] The test articles at 2, 4, 8 and 12-weeks were devoid of any microscopic tissue response, confirming the biocompatibility of this preparation. Upon injection, the test article appeared to integrate into the stromal elements of the dermis. Measurements of height and diameter were unchanged between 2 and 4 weeks. At 8-weeks CTA seemed to extend laterally in the dermal layers, but still maintained its volume. Conversely, the control article appeared as a homogeneous bolus of material compressing the underlying dermis. A minor macrophage infiltrate was observed in the control article at 4-weeks, and at 8-weeks most of the injection had resorbed from the injection site.

[0116] The in vivo stability of the test article at 8, and 12-weeks, compared to the control article indicates that this product can exhibit long-term persistence in clinical applications. These results support in vitro data above showing in vivo resistance to degradation by hyaluronidase.

[0117] While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

Example 21

Synergistic Effect of Lidocaine on Rheological Properties of the Gel

[0107] Lidocaine can have a synergistic effect and increase the initial storage modulus G' of the gel compared to otherwise identical compositions prepared in a buffer without lidocaine. Crosslinked HA of Example-5 was processed as in Example-12 using three separate phosphate buffers 1 (no lidocaine), 2 (0.2% lidocaine), and 3(0.3% lidocaine). Gels were made to 32-mg/mL concentrations and the storage modulus G' and degradation profile ΔG'/Δt of each was measured according to the method described in Example-12. **FIG. 7** shows that the compositions with lidocaine have a significantly higher modulus G' over the time of the test. Thus, crosslinked HA with lidocaine can have good biostability, and can in some cases have a synergistic effect, increasing G'.

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